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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,149	06/28/2005	John Aitken Graham	62130-0014	1569

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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,149	GRAHAM ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's amendment and arguments submitted April 4, 2008 wherein claim 4 is amended. This application is a national stage application of PCT/GB03/03562, filed August 18, 2003, which claims priority to foreign application GB0218811.8, filed August 14, 2002.

Claims 1-4 are pending in this application.

Claims 1-4 as amended are examined on the merits herein.

The following rejections of record in the precious office action are maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hille et al. (US patent 5705186, Of record in previous action) in view of Gao et al. (US patent publication 2003/0050257, Of record in previous action) in view of Remington. (Reference of record in previous action)

Hille et al. discloses transdermal compositions comprising morphine-6-glucuronide or its salts. (column 1, lines 45-55) Although all pharmaceutically acceptable salts are suitable for this invention, the hydrochloride salt is preferred.

(column 3, lines 22-25) Hille et al. does not disclose a hydrobromide salt of morphine-6-glucuronide.

Gao et al. discloses a number of glycosylated morphine derivatives, including 6-glucuronide adducts. (p. 1, paragraphs 0014-0021) Pharmaceutically acceptable salts of these compounds include the bromide salts. (p. 3, paragraph 0037)

Remington discloses that as part of the drug discovery process many different salts are prepared and evaluated. (p. 704, left column, second paragraph, right column, first and second paragraphs) During the process of salt selection various salt forms of a given active agent are explored and evaluated to determine which is the optimal form of the drug. Hydrobromide is listed as being a pharmaceutically acceptable counterion with pKa and ClogP similar to hydrochloride. (p. 704, table 2) Parameters that depend on the counterion include solubility, dissolution, hygroscopicity, stability, and processing. (p. 705, right column, fourth paragraph) Multitiered and decision-tree approaches to salt selection and evaluation are discussed. (p. 712, left paragraph fifth column – right paragraph third paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce morphine-6-glucuronide hydrobromide by substituting the known hydrochloride salt with the bromide ion. It is obvious for one of ordinary skill in the art to substitute one known element of a prior art invention for another, where the art suggests the substitution. In the instant case, Gao et al. discloses that the bromide ion is suitable as a counterion for similar pharmaceutical compounds, and furthermore, Remington discloses that it is typical and routine in the art to make and evaluate a number of

different salt forms of a given drug, including the hydrobromide form, in order to determine the optimal salt form for the desired application. Therefore one of ordinary skill in the art would have clearly been motivated to make and evaluate morphine-6-glucuronide hydrobromide as a pharmaceutical active agent. Furthermore, according to Pfizer v. Apotex (Fed. Cir. 2006-1261) in the case of a medicinal or pharmaceutical chemist developing an active agent for pharmaceutical use, "irrefutable evidence shows that a skilled chemist at the time would simply make known pharmaceutically-acceptable salts of whatever active ingredient with which he or she was working at the time." (p. 22, first paragraph) These salts would, as evidenced by Remington, include the hydrobromide salt, which was a known pharmaceutically acceptable salt at the time of the invention. With regard to the fact that the anion under consideration was not commonly used in pharmaceutical active agents, the court stated, "That benzene sulphonate was only used in creating 0.25% of FDA-approved drugs is not highly probative, much less dispositive. Indeed, beyond hydrochloride, which was used in approximately 43% of approved drugs, almost all other salts could be characterized as 'rarely used.'" (p. 22, second paragraph)

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted April 4, 2008, with respect to the above ground of rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that HIlle et al. teaches away from the claimed invention by reciting hydrochloride as a preferred salt species. According to MPEP 2123, disclosed examples and preferred embodiments do not constitute a

teaching away from a broader disclosure or nonpreferred embodiments. See In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." See In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) 27 F.3d at 554, 31 USPQ2d at 1132.). 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). In the instant case, Hille et al. does not actually teach away from the hydrobromide salt by presenting teachings that would lead one of ordinary skill in the art to discount other salts such as hydrobromide but merely the teaching that hydrochloride is a preferred embodiment of the invention.

Applicant further argues that Gao does not disclose any 6-glucuronide adducts of morphine. Gao is not relied on as an anticipatory reference, but merely as a secondary reference teaching bromine as a counterion to compounds similar in structure to morphine-6-glucuronide.

Applicant further argues that Remington does not teach that the hydrobromide salt is suitable or particularly useful for combination with morphine-6-glucuronide. However, what Remington does teach is the general process of evaluating various FDA-approved salts such as hydrobromide for utility as counterions of a particular drug. Given that hydrobromide is disclosed by both Gao and Remington as a salt that could be used as a counterion in the instant case, one of ordinary skill in the art would have easily been able to evaluate it and many other salts without undue or unpredictable experimentation.

Furthermore, According to the United States Court of Appeals for the Federal Circuit, in the case of *Pfizer vs. Apotex* (Cited above) with regard to a novel salt form of a known pharmaceutical, "The evidence shows that, upon making a new acid addition salt, it was routine in the art to verify the expected physicochemical characteristics of each salt, including solubility, pH, stability, hygroscopicity, and stickiness, and Pfizer's scientists used standard techniques to do so. These type of experiments used by Pfizer's scientists to verify the physicochemical characteristics of each salt are not equivalent to the trial and error procedures often employed to discover a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success. This is not to say that the length, expense, and difficulty of the techniques used are dispositive since many techniques that require extensive time, money, and effort to carry out may nevertheless be arguably "routine" to one of ordinary skill in the art. Rather, our conclusion here relies on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation." (p. 31, second paragraph) Thus it is clear that the routine procedures of counterion optimization carried out on a prior art pharmaceutical compound do not serve to impart patentability to a known product, and the time, money, and effort required to discover the optimal salt form for a particular use does not render that form patentable.

Finally, Applicant argues that the claimed salts possess unexpected stability compared to other prior art forms including the hydrochloride and the sulfate form. Again, this situation was addressed by the United States Court of Appeals for the

Federal Circuit, in *Pfizer vs. Apotex*. (Cited above) According to the court, with regard to an otherwise *prima facie* obvious salt form of a known pharmaceutical compound that had been shown to possess improved stability and shelf life over the prior art, "The district court wrongly relied on the fact that the "besylate salt works" because considerable evidence shows that amlodipine maleate also worked for its intended purpose and even did so in human clinical trials, even though somewhat inferior in ease of tableting and projected shelf-life. At most, then, Pfizer engaged in routine, verification testing to optimize selection of one of several known and clearly suggested pharmaceutically-acceptable salts to ease its commercial manufacturing and marketing of the tablet form of the therapeutic amlodipine." (P. 38, last paragraph) and "Amlodipine besylate is obvious on the facts of this case because the '909 patent suggested—and Dr. Wells expected—that every other potential salt form of amlodipine would be adequate for its intended purpose, i.e., to increase bioavailability of amlodipine, and would solve the stickiness problem of the maleate salt. The fact that amlodipine besylate was the best of the seven acid addition salts actually tested proves nothing more than routine optimization that would have been obvious to one of ordinary skill in the art." (p. 39, first paragraph) Also the court in DyStar, (464 F.3d at 1368) ruled that Creating a "product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient . . . to enhance commercial opportunities . . . is universal—and even common-sensical." Therefore Applicant's evidence of secondary considerations is not persuasive to overcome the *prima faice* case of obviousness.

For these reasons the rejection is deemed proper and made **FINAL**.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hille et al. (US patent 5705186, Of record in previous action) in view of Merrill et al. (US patent 5593695, Of record in previous action) in view of Remington. (Reference of record in previous action)

Hille et al. discloses transdermal compositions comprising morphine-6-glucuronide or its salts. (column 1, lines 45-55) Although all pharmaceutically acceptable salts are suitable for this invention, the hydrochloride salt is preferred. (column 3, lines 22-25) Hille et al. does not disclose a hydrobromide salt of morphine-6-glucuronide.

Merrill et al. discloses a pharmaceutical composition comprising morphine. (column 1, lines 35-47) Pharmaceutically acceptable forms or morphine include the hydrobromide salt. (column 1, line 58)

Remington discloses that as part of the drug discovery process many different salts are prepared and evaluated. (p. 704, left column, second paragraph, right column, first and second paragraphs) During the process of salt selection various salt forms of a given active agent are explored and evaluated to determine which is the optimal form of the drug. Hydrobromide is listed as being a pharmaceutically acceptable counterion with pKa and ClogP similar to hydrochloride. (p. 704, table 2) Parameters that depend on the counterion include solubility, dissolution, hygroscopicity, stability, and processing. (p. 705, right column, fourth paragraph) Multitiered and decision-tree approaches to salt

selection and evaluation are discussed. (p. 712, left paragraph fifth column – right paragraph third paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce morphine-6-glucuronide hydrobromide by substituting the known hydrochloride salt with the bromide ion. It is obvious for one of ordinary skill in the art to substitute one known element of a prior art invention for another, where the art suggests the substitution. In the instant case, Merrill et al. discloses that the bromide ion is suitable as a counterion for similar pharmaceutical compounds, and furthermore, Remington discloses that it is typical and routine in the art to make and evaluate a number of different salt forms of a given drug, including the hydrobromide form, in order to determine the optimal salt form for the desired application. Therefore one of ordinary skill in the art would have clearly been motivated to make and evaluate morphine-6-glucuronide hydrobromide as a pharmaceutical active agent. Furthermore, according to Pfizer v. Apotex (Fed. Cir. 2006-1261) in the case of a medicinal or pharmaceutical chemist developing an active agent for pharmaceutical use, "irrefutable evidence shows that a skilled chemist at the time would simply make known pharmaceutically-acceptable salts of whatever active ingredient with which he or she was working at the time." (p. 22, first paragraph) These salts would, as evidenced by Remington, include the hydrobromide salt, which was a known pharmaceutically acceptable salt at the time of the invention. With regard to the fact that the anion under consideration was not commonly used in pharmaceutical active agents, the court stated, "That benzene sulphonate was only used in creating 0.25% of FDA-approved drugs is not highly

probative, much less dispositive. Indeed, beyond hydrochloride, which was used in approximately 43% of approved drugs, almost all other salts could be characterized as 'rarely used.'" (p. 22, second paragraph)

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted April 4, 2008, with respect to the above ground of rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that HIlle et al. teaches away from the claimed invention by reciting hydrochloride as a preferred salt species. According to MPEP 2123, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. See In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." See In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) 27 F.3d at 554, 31 USPQ2d at 1132.). 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). In the instant case, Hille et al. does not actually teach away from the hydrobromide salt by presenting teachings that would lead one of ordinary skill in the art to discount other salts such as hydrobromide but merely the teaching that hydrochloride is a preferred embodiment of the invention.

Applicant further argues that Remington does not teach that the hydrobromide salt is suitable or particularly useful for combination with morphine-6-glucuronide. However, what Remington does teach is the general process of evaluating various FDA-approved salts such as hydrobromide for utility as counterions of a particular drug.

Given that hydrobromide is disclosed by both Gao and Remington as a salt that could be used as a counterion in the instant case, one of ordinary skill in the art would have easily been able to evaluate it and many other salts without undue or unpredictable experimentation.

Furthermore, According to the United States Court of Appeals for the Federal Circuit, in the case of *Pfizer vs. Apotex*,(Cited above) with regard to a novel salt form of a known pharmaceutical, "The evidence shows that, upon making a new acid addition salt, it was routine in the art to verify the expected physicochemical characteristics of each salt, including solubility, pH, stability, hygroscopicity, and stickiness, and Pfizer's scientists used standard techniques to do so. These type of experiments used by Pfizer's scientists to verify the physicochemical characteristics of each salt are not equivalent to the trial and error procedures often employed to discover a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success. This is not to say that the length, expense, and difficulty of the techniques used are dispositive since many techniques that require extensive time, money, and effort to carry out may nevertheless be arguably "routine" to one of ordinary skill in the art. Rather, our conclusion here relies on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation." (p. 31, second paragraph) Thus it is clear that the routine procedures of counterion optimization carried out on a prior art pharmaceutical compound do not serve to impart patentability to a

known product, and the time, money, and effort required to discover the optimal salt form for a particular use does not render that form patentable.

Finally, Applicant argues that the claimed salts possess unexpected stability compared to other prior art forms including the hydrochloride and the sulfate form. Again, this situation was addressed by the United States Court of Appeals for the Federal Circuit, in *Pfizer vs. Apotex*. (Cited above) According to the court, with regard to an otherwise *prima facie* obvious salt form of a known pharmaceutical compound that had been shown to possess improved stability and shelf life over the prior art, "The district court wrongly relied on the fact that the "besylate salt works" because considerable evidence shows that amlodipine maleate also worked for its intended purpose and even did so in human clinical trials, even though somewhat inferior in ease of tableting and projected shelf-life. At most, then, Pfizer engaged in routine, verification testing to optimize selection of one of several known and clearly suggested pharmaceutically-acceptable salts to ease its commercial manufacturing and marketing of the tablet form of the therapeutic amlodipine." (P. 38, last paragraph) and "Amlodipine besylate is obvious on the facts of this case because the '909 patent suggested—and Dr. Wells expected—that every other potential salt form of amlodipine would be adequate for its intended purpose, i.e., to increase bioavailability of amlodipine, and would solve the stickiness problem of the maleate salt. The fact that amlodipine besylate was the best of the seven acid addition salts actually tested proves nothing more than routine optimization that would have been obvious to one of ordinary skill in the art." (p. 39, first paragraph) Also the court in DyStar, (464 F.3d at 1368) ruled that

Creating a "product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient . . . to enhance commercial opportunities . . . is universal—and even common-sensical." Therefore Applicant's evidence of secondary considerations is not persuasive to overcome the *prima faice* case of obviousness.

For these reasons the rejection is deemed proper and made **FINAL**.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hille et al. (US patent 5705186, Of record in previous action) in view of Berge et al. (Reference of record in previous action) in view of Remington. (Reference of record in previous action)

Hille et al. discloses transdermal compositions comprising morphine-6-glucuronide or its salts. (column 1, lines 45-55) Although all pharmaceutically acceptable salts are suitable for this invention, the hydrochloride salt is preferred. (column 3, lines 22-25) Hille et al. does not disclose a hydrobromide salt of morphine-6-glucuronide.

Berge et al. discloses a number of commercially marketed pharmaceutically acceptable salts. (p. 2, table I) The hydrobromide salt is included as a pharmaceutically acceptable salt.

Remington discloses that as part of the drug discovery process many different salts are prepared and evaluated. (p. 704, left column, second paragraph, right column, first and second paragraphs) During the process of salt selection various salt forms of a

given active agent are explored and evaluated to determine which is the optimal form of the drug. Hydrobromide is listed as being a pharmaceutically acceptable counterion with pKa and ClogP similar to hydrochloride. (p. 704, table 2) Parameters that depend on the counterion include solubility, dissolution, hygroscopicity, stability, and processing. (p. 705, right column, fourth paragraph) Multitiered and decision-tree approaches to salt selection and evaluation are discussed. (p. 712, left paragraph fifth column – right paragraph third paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce morphine-6-glucuronide hydrobromide by substituting the known hydrochloride salt with the bromide ion. It is obvious for one of ordinary skill in the art to substitute one known element of a prior art invention for another, where the art suggests the substitution. In the instant case, Berge et al. discloses that the hydrobromide salt is suitable as a counterion for pharmaceutical compounds, and furthermore, Remington discloses that it is typical and routine in the art to make and evaluate a number of different salt forms of a given drug, including the hydrobromide form, in order to determine the optimal salt form for the desired application. Therefore one of ordinary skill in the art would have clearly been motivated to make and evaluate morphine-6-glucuronide hydrobromide as a pharmaceutical active agent. Furthermore, according to Pfizer v. Apotex (Fed. Cir. 2006-1261) in the case of a medicinal or pharmaceutical chemist developing an active agent for pharmaceutical use, "irrefutable evidence shows that a skilled chemist at the time would simply make known pharmaceutically-acceptable salts of whatever active ingredient with which he or she was working at the

time." (p. 22, first paragraph) These salts would, as evidenced by Remington, include the hydrobromide salt, which was a known pharmaceutically acceptable salt at the time of the invention. With regard to the fact that the anion under consideration was not commonly used in pharmaceutical active agents, the court stated, "That benzene sulphonate was only used in creating 0.25% of FDA-approved drugs is not highly probative, much less dispositive. Indeed, beyond hydrochloride, which was used in approximately 43% of approved drugs, almost all other salts could be characterized as 'rarely used.'" (p. 22, second paragraph)

Therefore the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted April 4, 2008, with respect to the above ground of rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that HIlle et al. teaches away from the claimed invention by reciting hydrochloride as a preferred salt species. According to MPEP 2123, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. See In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." See In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) 27 F.3d at 554, 31 USPQ2d at 1132.). 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). In the instant case, Hille et al. does not actually teach away from the hydrobromide salt by presenting teachings that would lead

one of ordinary skill in the art to discount other salts such as hydrobromide but merely the teaching that hydrochloride is a preferred embodiment of the invention.

Applicant further argues that Remington does not teach that the hydrobromide salt is suitable or particularly useful for combination with morphine-6-glucuronide. However, what Remington does teach is the general process of evaluating various FDA-approved salts such as hydrobromide for utility as counterions of a particular drug. Given that hydrobromide is disclosed by both Gao and Remington as a salt that could be used as a counterion in the instant case, one of ordinary skill in the art would have easily been able to evaluate it and many other salts without undue or unpredictable experimentation.

Furthermore, According to the United States Court of Appeals for the Federal Circuit, in the case of *Pfizer vs. Apotex*,(Cited above) with regard to a novel salt form of a known pharmaceutical, "The evidence shows that, upon making a new acid addition salt, it was routine in the art to verify the expected physicochemical characteristics of each salt, including solubility, pH, stability, hygroscopicity, and stickiness, and Pfizer's scientists used standard techniques to do so. These type of experiments used by Pfizer's scientists to verify the physicochemical characteristics of each salt are not equivalent to the trial and error procedures often employed to discover a new compound where the prior art gave no motivation or suggestion to make the new compound nor a reasonable expectation of success. This is not to say that the length, expense, and difficulty of the techniques used are dispositive since many techniques that require extensive time, money, and effort to carry out may nevertheless be arguably "routine" to

one of ordinary skill in the art. Rather, our conclusion here relies on the fact that one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation." (p. 31, second paragraph) Thus it is clear that the routine procedures of counterion optimization carried out on a prior art pharmaceutical compound do not serve to impart patentability to a known product, and the time, money, and effort required to discover the optimal salt form for a particular use does not render that form patentable.

Finally, Applicant argues that the claimed salts possess unexpected stability compared to other prior art forms including the hydrochloride and the sulfate form. Again, this situation was addressed by the United States Court of Appeals for the Federal Circuit, in *Pfizer vs. Apotex*. (Cited above) According to the court, with regard to an otherwise *prima facie* obvious salt form of a known pharmaceutical compound that had been shown to possess improved stability and shelf life over the prior art, "The district court wrongly relied on the fact that the "besylate salt works" because considerable evidence shows that amlodipine maleate also worked for its intended purpose and even did so in human clinical trials, even though somewhat inferior in ease of tableting and projected shelf-life. At most, then, Pfizer engaged in routine, verification testing to optimize selection of one of several known and clearly suggested pharmaceutically-acceptable salts to ease its commercial manufacturing and marketing of the tablet form of the therapeutic amlodipine." (P. 38, last paragraph) and "Amlodipine besylate is obvious on the facts of this case because the '909 patent suggested—and Dr. Wells expected—that every other potential salt form of amlodipine would be

adequate for its intended purpose, i.e., to increase bioavailability of amlodipine, and would solve the stickiness problem of the maleate salt. The fact that amlodipine besylate was the best of the seven acid addition salts actually tested proves nothing more than routine optimization that would have been obvious to one of ordinary skill in the art." (p. 39, first paragraph) Also the court in DyStar, (464 F.3d at 1368) ruled that Creating a "product or process that is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient . . . to enhance commercial opportunities . . . is universal—and even common-sensical." Therefore Applicant's evidence of secondary considerations is not persuasive to overcome the *prima faice* case of obviousness.

For these reasons the rejection is deemed proper and made **FINAL**.

Conclusion

No claims are allowed in this application. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/
Examiner, Art Unit 1623
7/31/2008

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623